



Outcome in neonates with necrotizing enterocolitis and patent ductus arteriosus

Journal:	<i>World Journal of Pediatrics</i>
Manuscript ID:	WJP-2014-0403.R3
Manuscript Type:	Original Article
Keywords:	Necrotizing enterocolitis, Patent ductus arteriosus, Mortality
Specialty Area:	Neonatology, Congenital heart diseases, Critical Care

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Abstract

Background: Since there is no agreement of the influence of patent ductus arteriosus (PDA) on outcome in necrotizing enterocolitis (NEC), we assessed the influence of PDA on NEC outcomes.

Methods: A retrospective study of 131 infants with established NEC was performed. Outcome (death, disease severity, need for surgery, hospitalization duration), as well as multiple clinical parameters were compared between patients with NEC with no congenital heart disease (n=102) and those with an isolated PDA (n=29). Univariate, multivariate as well as stepwise logistic regression analyses were performed (SPSSv19).

Results: Birth weight and gestational age were significantly lower in patients with PDA (1120g (1009- 1562g, median [CI95]), 28.4w (27.8- 30.5w)) as compared to patients without PDA (1580g (1593- 1905g), 32.4w (31.8- 33.5w); p<0.05). The risk of NEC- attributable fatality was higher in NEC with PDA (35%) as compared to NEC without PDA (14%) (univariate OR 3.3, CI95 1.8- 8.6, p<0.05; however multivariate OR 2.4, CI95 0.82- 2.39; P=0.111). Significant independent predictors for non-survival within the entire cohort were advanced disease severity stage III (OR 27.9, CI95 7.4- 105, p<0.001) and birth weight below 1100g (OR 5.7, CI95 1.7- 19.4, p<0.01).

Conclusions:

In patients with NEC, the presence of a PDA was associated with an absolute increased risk of death. However when important differences between the two study groups were controlled for, only birth weight and disease severity independently predicted mortality.

KEY WORDS: Necrotizing enterocolitis; patent ductus arteriosus; congenital heart disease; neonatal mortality.

Introduction

Since the first description of cardiogenic necrotizing enterocolitis in 5 patients with underlying congenital heart disease (CHD) by Polin and coworkers in 1976,^[1] there is increasing evidence that cardiogenic necrotizing enterocolitis is a distinct disease entity from NEC in the otherwise healthy preterm grower and feeder.^[2,3] Within the group of neonates with heart failure those who are

premature with an isolated patent ductus arteriosus (PDA) are suggested to represent another subgroup of NEC, differing from those patients with other forms of CHD.^[4]

The presence of NEC has had an unclear effect on the mortality of patients with CHD.^[5-7] Conflicting results are equally encountered in neonates with PDA. On the one hand, NEC patients with PDA were found to have better outcomes as compared to NEC patients without PDA.^[3] On the other hand PDA was described to be associated with increased mortality in NEC patients.^[8] However the latter studies include suspected NEC,^[3, 8] potentially biasing outcome results due to the generally better outcome in patients with suspected NEC as compared to patients with proven NEC. Thus the question remains; in patients with NEC, does the presence of a PDA increase the risk of a worse outcome?

The primary aim of the present study was to assess the risk for adverse outcome between patients with established NEC with or without PDA. We hypothesized that NEC outcomes vary according to the presence of PDA.

Methods

We retrospectively assessed data from an institutional database of infants with the diagnosis of acute NEC in a single tertiary perinatal center (Inselspital, University Hospital and University of Bern, Switzerland) over a 30 year period between January 1981 and October 2011 (n= 196). Data analysis was preceded by local ethics committee approval. After exclusion of 65 patients with CHD other than PDA, spontaneous intestinal perforation, and suspected NEC (Bell stage I^[9]) the datasets for 131 patients with confirmed NEC (Bell stage II or III) remained for final analysis. Bell staging was performed by review of patient charts including radiographies by 3 independent senior physicians (UK, DC, MN, PK, SB).^[9] Patients were admitted to the PDA group if clinical and echocardiography findings concluded that there was a moderate or severe PDA.

Primary outcome- variables were defined as death due to NEC, disease severity as defined by Bell-stage,^[9] need for surgery, and duration of hospital stay. Further analyzed variables were: Gestational age (GA, weeks (w)), birth weight (BW, grams (g)), percentile weight at birth (%), gender, twin birth, presence of perinatal asphyxia, need for postnatal intravenous sympathomimetic drugs, feeding habits (given as no enteral feeding from birth until the onset of NEC (NPO)), formula feeding alone, or both formula and maternal milk (MM)), age at disease onset (d), routine laboratory parameters at disease

onset (white blood cell count (G/l), IT-ratio (%), hemoglobin concentration (g/l), platelet count (G/l), lactate concentration (mg/l)), treatment (surgical, medical), time from disease onset to surgery (in surgical patients), need for a stoma, length of bowel affected, isolated small bowel affected, small bowel and colon affected, only colon affected, and histologic analysis from resections for acute disease. Hematoxylin and eosin- stained slides were assessed by two blinded independent senior physicians (SS, UK) in a total of 32 patients. After omission of 7 cases due the quality of the specimens, analysis was performed in specimen of 21 patients without CHD and 4 patients with PDA. Intestinal inflammation and coagulation necrosis were both graded from 0 to 4 according to Balance and coworkers.^[10] Results are reported as principally inflammatory or principally coagulation- necrotic if difference in grading was ≥ 1 point for the respective pathological finding.

SPSS vers 19 (IBM, SPSS, Chicago, IL, USA) was used for statistical analysis. Data were tested for normality and equal distribution via the Kolmogorov-Smirnov test and were assessed for skewness and kurtosis. Comparisons between groups were performed using analysis of variance (ANOVA) with Bonferroni- and Dunnett-T3- post-hoc analysis, student's T-Test or non-parametric tests (as required, respectively) for continuous variables as well as Chi-square or Fisher's exact test (as required, respectively) for categorical variables.

To assess the influence of PDA uni- and multivariate logistic regression analyses were performed for each outcome parameter. The continuous outcome variable, the length of hospital stay in survivors, was transformed into a categorical variable using receiving operator characteristics (ROC) analysis for discrimination between patients without PDA and with PDA. ROC analysis resulted in an optimal cut-off of 65d with a discriminative sensitivity of 70%, a specificity of 68%, and an area under the curve (AUC) of 61% (54- 81% [CI95]). Multivariate regression was adjusted for birth weight, gestational age, age at onset of NEC, and birth year. Independent predictors for non- survival were identified using a binary stepwise logistic regression model. Ideal birth weight cut-off was identified at 1100g (AUC 76%, CI95 66- 86%). Data are given as adjusted odds ratio (OR), or median and 95% confidence interval of the mean (CI95) for continuous variables, and as percent frequencies for categorical variables unless otherwise specified. Two- sided tests were used throughout. $P<0.05$ was considered significant.

Results

Out of a total of 131 included patients with confirmed NEC stage Bell II or III, 102 had NEC without PDA and 29 patients had a moderate to severe PDA.

BW and GA were significantly different between patient groups (Table 1). BW and GA were lower in PDA patients (1120g [1009- 1562g], 28.4w [27.8- 30.5w], median [CI95], respectively) than in patients without PDA (1580g [1593- 1905g], 32.4w [31.8- 33.5w]) ($p<0.05$, respectively). There was a non- significant trend for a higher rate of postnatal administration of sympathomimetic agents in PDA patients (30.8%) than in non-PDA patients (13.4%).

In patients without PDA age at diagnosis was lower (7 days, 8.4- 12.8) as in patients with PDA (14 days, 11.4- 21.7, $p<0.01$, Table 2). Hemoglobin concentration at diagnosis was higher in patients without PDA (160 g/l, 153- 167) as compared to patients with PDA (146 g/l, 131- 154, $p<0.05$).

There were no differences regarding surgical findings between patient groups (data not shown).

Histologic grading resulted in equal proportions for inflammation (50%) versus necrosis (50%) in patients with PDA, while in patients without PDA, there was a slight preponderance towards inflammation (62%) against coagulation necrosis (38%), however without statistical significance for differences between groups.

NEC- attributable mortality was significantly elevated in patients with PDA (34.5%) as compared to patients without PDA (13.7%; $p<0.05$). Univariate odds ratio for non- survival was significantly higher in the presence of a PDA (OR, CI95: 3.3, 1.8- 8.6; $p=0.014$, Table 3). This increased risk of mortality did not hold true when important differences between the two groups were controlled for (multivariate OR 2.4, CI95 0.82- 2.39; $P=0.111$). Multivariate regression showed that birth year did neither influence the odds of death nor the length of hospital stay in PDA (Table 3). However birth weight and gestational age assimilated the statistical significance of both, the risk of death and the length of hospital stay in PDA (Table 3). Accordingly a birth weight below 1100g represented a significant independent predictor for non- survival as did advanced NEC stage (Table 4). Eight infants developed proven intestinal strictures, none of them having underlying PDA (not significant).

Outcome parameters were not different between PDA patients receiving indometacin for PDA closure before onset of NEC ($n=4$) and those not receiving indometacin treatment before disease onset ($n=25$).

Discussion

The main result of the present investigation is that we found a trend towards worse outcome in NEC patients if they had a patent ductus arteriosus (PDA). The present study is to the best of our knowledge the first investigation comparing patients with an established NEC (Bell stage \geq II) without PDA (or other congenital heart failure) to NEC patients with isolated PDA. There is only one study comparing outcome parameters between NEC in patients without a PDA and in those with a PDA reporting better outcomes in infants with PDA.^[3] In contrast to the named work of Pickard et al we omitted a major inclusion bias in the present study by only including confirmed NEC cases. Pickard et al potentially flawed their results since 36% of their patients with PDA had NEC stage I while only 19% in the non-PDA group had NEC stage I.^[3] The higher rate of "unconfirmed", or "suspected" NEC cases in their PDA- group might be an explanation for the better outcome of patients in the PDA- group, supposing that outcome in suspected NEC stage I would be better than in confirmed NEC, stage II or III. We conclude that the presence of a PDA does not improve outcome in patients with confirmed NEC with a mortality risk that increases from 14% in patients without PDA to 35% in patients with PDA. However higher mortality risk in PDA patients was only significant in univariate analysis. When important differences between the two study groups were controlled for by means of multivariate analysis, this effect was not statistically significant.

Above that, we found further significant differences between non- PDA and PDA NEC patients supporting the hypothesis of different disease entities: First, gestational age and birth weight were lower in patients with PDA. This observation is in accordance with the results from Pickard and coworkers.^[3] Second age at disease onset was higher in the PDA group (median 14d) as compared to the non- PDA group (median 7d, $P<0.05$). This finding is in accordance with the data reported from Gonzalez-Rivera and colleagues, who describe an inverse correlation between timing of disease onset and gestational age.^[11] Pickard et al.^[3] describe about equivalent medians for disease onset in NEC without (10d) and with PDA (14d) as compared to our data. Third, we found a non-significant trend towards more histologic intestinal inflammation in non- PDA NEC, supporting different pathophysiological disease entities. To the best of our knowledge, we did not find another report comparing intestinal inflammation and coagulative necrosis in NEC patients with or without PDA.

Nevertheless, it is well known that abdominal aortic flow reversal is associated with an increased risk for NEC.^[12] Unfortunately the trend towards intestinal inflammation in non- PDA NEC could neither be confirmed by different levels of laboratory parameters at disease onset nor by macroscopic intraoperative findings.

An argument against an etiopathologic contribution of PDA to intestinal ischemia and disease outcome is our finding that PDA was not an independent predictor for non- survival in stepwise multivariate regression analysis in contrast to disease severity and birth weight.

Our study has several limitations. The retrospective study design engenders several potential sources for bias. In addition the long inclusion period over 30 years bears a multitude of possible confounders flawing results as e.g. changing intensive care protocols, other feeding habits, and different surgical approaches. We however feel that the duration of inclusion did not have a major influence on the assessed outcome parameters since inclusion of birth year in multivariate analysis did not change the risk for mortality. Additionally, other investigators have found that mortality was stable in a study of 360 NEC patients between 1986 and 1999 which supports our findings.^[13] Also we present a relatively small number of PDA patients resulting in relatively low statistical power. And the results on mortality are not statistically significant in multivariate analysis. The finding that the presence of a PDA does not worsen outcome in patients with NEC is in line with the results of the only study with a similar number of patients with confirmed NEC by Pickard et al. Finally we do not have data on flow parameters, the ultimate proof of intestinal circulatory disturbance. However it was not the primary aim of the study to elucidate disease etiologies in NEC with PDA. Taken altogether we advocate prospective multicenter assessment of NEC related outcomes.

We conclude that in patients with established necrotizing enterocolitis, the presence of a patent ductus arteriosus was associated with an absolute increased risk for longer hospital stay and death. However, when important differences between the two study groups were controlled for, only disease severity and birth weight independently predicted mortality.

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Tables

Table 1: Comparison of perinatal characteristics in NEC patients with patent ductus arteriosus and patients without patent ductus arteriosus.

Variable	no PDA (n=102)	PDA (n=29)	P
Gestational age, w (CI95)	32.4 (31.8-33.5)	28.4 (27.8-30.5)	<0.001
Birth weight, g (CI95)	1580 (1593-1905)	1120 (1009-1562)	.001
Percentile weight, % (CI95)	15 (25-38)	35 (23-52)	NS
Asphyxia, n (%)	5 (4.9)	0 (0)	NS
Twin, n (%)	16 (15.7)	4 (13.8)	NS
Female, n (%)	54 (53.5)	12 (41.4)	NS
Sympathomim., n (%)	13 (13.4)	8 (30.8)	NS
NPO, n (%)	1 (1.2)	2 (8.7)	NS
Formula alone, n (%)	16 (19)	4 (17.4)	NS
MM and formula, n (%)	36 (42.9)	49 (39.1)	NS

Data are n (% within the respective group) for categorical variables, and median (95% confidence interval) for continuous variables. PDA, patent ductus arteriosus; Sympathomim., postnatal need for intravenous sympathomimetic drugs; feeding details are given as no enteral feeding from birth until the onset of NEC (NPO), formula feeding alone, or both formula and maternal milk (MM).

Table 2: Disease presentation, and initial laboratory parameters in NEC patients with and without patent ductus arteriosus.

Variable	no CHD (n=102)	PDA (n=29)	P
Age at disease onset, d (CI95)	7.0 (8.4- 12.8)	14.0 (11.4-21.7)	.006
Bloody stools, n (%)	65 (69.1)	13 (56.5)	NS
Leukocyte count, G/l (CI95)	9.9 (10.5- 13.4)	12.2 (9.4- 15.1)	NS
IT-ratio, % (CI95)	10.0 (10.7- 16.6)	15.8 (12.0- 25.4)	NS
Platelet count, G/l (CI95)	241 (233-290)	298 (224- 337)	NS
Hemoglobin, g/l (CI95)	160 (153- 167)	146 (131- 154)	.012
CRP, mg/dl (CI95)	0 (5.3- 16.6)	0 (1.0- 12.9)	NS
Lactate level, n (%)	1.9 (1.9- 3.2)	2.3 (1.4- 5.4)	NS

Data are n (% within the respective group) for categorical variables, and median (95% confidence interval [CI]) for continuous variables. CHD, congenital heart disease; PDA, patent ductus arteriosus; IT- ratio, immature to total ratio; hemoglobin, hemoglobin concentration; CRP, C- reactive protein.

Table 3: Uni- and multivariate risk of adverse outcome in NEC- with patent ductus arteriosus and patients without patent ductus arteriosus.

Outcome	no PDA n=102	PDA n=29	Univariate OR (95% CI), P	Multivariate OR ^a (95% CI), P	Multivariate OR ^b (95% CI), P
Death due to NEC, n (%)	14 (13.7)	10 (34.5)	3.31	3.31	2.39
Bell stage III, n (%)	18 (17.6)	7 (24.1)	1.49	1.49	0.67
Need for surgery, n (%)	46 (45.1)	16 (55.2)	1.26	1.22	0.67
Hospitalization 65days	34 (44.1)	22 (75.9)	3.98	4.65	2.1
in survivors ^c , n (%)			(1.56- 10.2), .004	(1.68-12.84), .003	(0.68-6.46), .198

Data are n (%) within the respective group) for categorical variables, and median (95% confidence interval [CI]) for continuous variables. OR, odds ratio; PDA, patent ductus arteriosus. ^a Adjustment of the multivariate model includes birth year. ^b Adjustment of the multivariate model includes gestational age (GA) and birth weight (BW). ^c The cutoff of 65 days was chosen according to receiving operator characteristics curve analysis for comparison of duration of hospitalization between patients with or without PDA.

Table 4: Independent predictors for non- survival in infants with necrotizing enterocolitis according to stepwise regression analysis.

Variable	OR	95% CI	P
Bell stage III	27.92	7.39- 105	.000
Birth weight \leq 1100g ^a	5.69	1.67- 19.4	.005
Birth year	1.079	1.02- 1.15	.013

OR, odds ratio PDA, patent ductus arteriosus, ^c The cutoff of 65 days was chosen according to receiving operator characteristics curve analysis for comparison of birth weight between survivors and non- survivors.